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Are Inflammatory Cytokines Associated with Pain during Acute Myocardial Infarction?

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Keywords

Acute myocardial infarction · Cardiovascular disease · Pain · Cytokines · Inflammation · Posttraumatic stress · Psychological stress

Abstract

Objective: Pain and inflammation during acute myocardial infarction (AMI) have been associated with the development of posttraumatic stress disorder and may also impact negatively on somatic outcome. We investigated the relationship between pain during AMI and levels of circulating proinflammatory (tumor necrosis factor [TNF]-α, interleukin [IL]-6) and anti-inflammatory (IL-33 and tissue growth factor [TGF]-β_1) cytokines. ***Methods:*** Data were collected as part of the Myocardial Infarction – Stress Prevention Intervention (MI-SPRINT) study. We included 140 patients (mean age 59.6 years, 82.1% male) with high acute psychological distress within 48 h after MI. Fasting blood samples were drawn thereafter to measure cytokine levels. Sociodemographic factors, psychological and medical data, as well as cardiometabolic markers were assessed with questionnaires and patient interviews. ***Results:*** Linear regression models showed a significant positive correlation of pain with TGF-β_1 ($b = 770.91$, $p = 0.031$) and a significant inverse correlation of pain with IL-33 ($b = –0.11$, $p = 0.015$) after controlling for age, gender, body mass index, lifetime depression, acute stress disorder symptoms, and the prognostic Global Registry of Acute Coronary Events (GRACE) score. Pain was not associated with IL-6 but with the GRACE score ($b = 0.01$, $p = 0.003$). Pain showed no significant association with TNF-α. ***Conclusion:*** Pain during MI was associated with anti- but not proinflammatory cytokines. As IL-33 has been shown to be cardioprotective, lower IL-33 levels with more intense pain may suggest a pathway through which increased pain during MI may have an impact on the medical prognosis.

Clinical trial registration No. NCT01781247 (ClinicalTrials.gov).

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Introduction

Acute myocardial infarction (AMI) is a life-threatening event during which the majority of patients experience intense pain [1]. Pain intensity has been shown to be associated with peritraumatic psychological distress [1] and the development of posttraumatic stress in patients who suffered MI [2–5]. Further, pain intensity seems to be associated with the clinical outcome in the aftermath of MI. A previous study showed that patients who had experienced more pain during MI also had a higher risk of hospital readmission due to cardiovascular disease events during a 32-month follow-up [6]. Therefore, pain during MI may be associated with a poorer prognosis regarding mental and physical health.

Due to hypoxic tissue damage and cell death, several pro- and anti-inflammatory processes are triggered during AMI. In a first step, an inflammatory reaction serves to process and clear damaged tissue [7]. During this process, proinflammatory cytokines like tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 are expressed [8]. In a second step, inflammation suppression facilitates initiation of myofibroblast proliferation and scarring. Molecules of the transforming growth factor (TGF)-β family play an important role in regulating this process [8, 9]. Another cytokine that is involved in cardiac remodeling is IL-33: it reduces MI volume and improves contractile function [10]. Although proinflammatory effects have also been attributed to IL-33, IL-33 appears to be atheroprotective and might thereby oppose cardiovascular disease progression [11]. In this paper, we will discuss IL-33 as an anti-inflammatory cytokine based on investigations in cardiological patients.

Not only cardiac tissue injury, but also pain intensity and psychological distress may cause an increase in inflammation markers during AMI. Both acute and chronic psychosocial stress have been associated with the release of proinflammatory cytokines, e.g., TNF-α and IL-6 [12–15], and, as mentioned above, pain and acute psychological distress are correlated during AMI.

Proinflammatory cytokines have been associated with impaired psychological and physical health in the long-term, including posttraumatic stress [16–19]. In population-based studies, IL-6 and TNF-α were both found to be associated with increased morbidity and mortality independent of other risk factors, particularly in men [20–22]. Several studies showed an association between worse cardiovascular outcome and increased TNF-α [23] and IL-6 [24–26] levels specifically following an acute coronary syndrome (ACS). However, despite their anti-inflammatory properties during MI, both IL-33 [27, 28] and TGF-β [29] have been found to be associated with a worse prognosis in coronary artery disease.

To date, little is known about the interplay of pain and myocardial damage regulating inflammation in AMI. Since pain and inflammation are both predictors of future cardiovascular and psychological health, we examined their relationship during AMI. We hypothesized that stronger pain during AMI would be associated with increased levels of proinflammatory cytokines TNF-α and IL-6, independent of sociodemographic, medical, and psychometric data. Furthermore, we expected a negative association between pain and the anti-inflammatory TGF-β_1 and IL-33.

Patients and Methods

Patients and Study Design

The present study retrieved data from the randomized-controlled trial Myocardial Infarction – Stress Prevention Intervention (MI-SPRINT), which was conducted between 2012 and 2015. The trial included patients who were referred to the Inselspital, Bern University Hospital, with AMI, and aimed to test whether trauma-focused psychological counseling in this phase could reduce the development of posttraumatic stress [30]. The study protocol was approved by the ethics committee of the State of Bern, Switzerland, and written informed consent was obtained from all participants. In addition to confirmed ST elevation MI (STEMI) or non-STEMI, further inclusion criteria were age ≥18 years, sufficient knowledge of the German language, stable circulatory conditions, and considerable pain and psychological distress during MI (cf. Psychometric Assessments). Specific exclusion criteria were severe comorbidity reducing life expectancy to <1 year, current severe depression per the cardiologist's clinical judgment, suicidal ideations during the last 2 weeks, cognitive impairment/disorientation, emergency coronary artery bypass graft surgery, and participation in another randomized, controlled clinical trial.

Within 48 h after hospital admission, participants underwent a standardized interview for the assessment of pain perception, medical history, and sociodemographic data. They also completed the Acute Stress Disorder Scale (ASDS). The following morning, a fasting blood sample was drawn to measure circulating biomarker concentrations.

Of 190 patients included, cytokine levels were assessable in 143. The most common reasons for missing values were the following: unexpected/immediate transfer to other hospitals, blood samples could not be processed on weekends, blood sampling was technically not possible, blood samples or values were lost, or blood samples were contaminated. In 3 cases, pertinent personal history data were lacking due to an unexpected transfer during their hospital stay. Data analysis could therefore be conducted on a final sample of 140 patients.

Demographic and Medical Factors

We obtained patient characteristics, including age, sex, living status, weight and height (to calculate the body mass index [BMI]); and medical history by standardized interview questions during

admission or from hospital charts. Medical information on the number of vessels involved in coronary lumen stenosis >50%, troponin T peak levels, left ventricular ejection fraction, and other parameters necessary to calculate the Global Registry of Acute Coronary Events (GRACE) score was retrieved from hospital charts.

The GRACE Score

The online tool "GRACE 2.0 ACS Risk Calculator" based on the revised GRACE algorithms for predicting death or death/myocardial infarction following an initial ACS [31] was used to calculate the GRACE score. The algorithm considers age, heart rate, systolic blood pressure, Killip class (indicating heart failure in AMI patients, [32]), initial serum creatinine concentration, positive initial cardiac markers, cardiac arrest on admission, and presence of ST deviation. A score is generated which is related to the occurrence of the named adverse outcomes with higher scores indicating higher risk of occurrence.

Psychometric Assessment

Pain and Acute Psychological Distress

Patients were asked to evaluate their most intense pain level experienced during AMI ("Please indicate how strong your pain was during the heart attack") on a scale from 0 to 10, with 10 being the highest imaginable pain (visual analogue scale for pain [33]). For inclusion in MI-SPRINT, a score of at least 5 for experienced pain and of at least 5 for either fear of dying ("During my referral to the hospital, the emergency unit, or the intensive care unit, I was afraid I was dying") and/or helplessness ("When the doctor told me I had a heart attack, I was frightened, felt helpless, and was afraid of losing control of the situation") was required.

ASD Symptoms

The German version of the ASDS was used to assess symptoms of ASD [34, 35]. The scale is a self-rating instrument with 19 items to be scored on a 5-point Likert scale, from 0 (not at all) to 4 (extremely). Sum scores range from 0 to 76, with higher values indicating more stress. The ASDS consists of the 4 subscales dissociation, reexperiencing, avoidance, and arousal (DSM IV) [36]. All participants were asked to rate these symptoms with respect to MI. The instrument was validated in a cardiac sample and showed good internal consistency (Cronbach α sum score = 0.88) [35]. Good reliability was also achieved in our sample (Cronbach α sum score = 0.84).

Laboratory Analysis

Blood samples were collected into EDTA tubes and centrifuged for 10 min at 2,000 *g*. Plasma was transferred to polypropylene tubes and stored at –80°C. Concentrations of biomarkers were determined using Luminex technology with magnetic bead-based immunoassays (human Th17 cytokine panel and TNF-α, IL-6, IL-33, TGF-β, and TGF-β_1 assays; Bio-Rad Laboratories Inc., Hercules, CA, USA). Intra- and interassay coefficients of variation were <10% for all biomarkers. Detection limits were 0.07 pg/mL (TNF-α), 0.67 pg/mL (IL-6), 0.58 pg/mL (IL-33), and 3.9 pg/mL (TGF-β_1). The levels of lowest quantification (LLOQ) were as follows: 0.57 pg/mL (TNF-α), 1.65 pg/mL (IL-6), 4.18 pg/mL (IL-33), and 1.69 pg/mL (TGF-β_1). Fluorescence intensity results were used to distinguish nondetectable from nonquantifiable values. Values below sensitivity (not detectable) were substituted with half the detection limit. Values between sensitivity and LLOQ (not quantifiable) were substituted with half the LLOQ.

Table 1. Characteristics of the patients stratified by pain severity

Variables	Total	Pain score		*p*
		5–7	8–10	
Patients, *n*	140	52	88	
%	100	37.1	62.9	
Mean age, years	59.6	58.7	60.1	0.47
Female gender, %	17.9	11.5	21.6	0.13
Mean BMI	27.3	27.2	27.3	0.33
Living alone, %	27.9	13.4	36.4	<0.01
Previous MI, %	8.6	5.8	10.2	0.36
Depression, %	26.4	23.1	28.4	0.49
Vessels involved, %				0.28
0 vessels	1.4	3.8	0	
1 vessel	36.4	38.5	35.2	
2 vessels	30.7	26.9	33.0	
3 vessels	31.4	30.8	31.8	
LVEF, %	47.4	47.6	47.3	0.89
Troponin T, μg/L	4.0	3.3	4.3	0.11
GRACE score	107.6	106.3	108.4	0.82

Peak troponin T and lifetime depression are listed. BMI, body mass index; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Statistical Analysis

Data were analyzed using the PASW 21.0 statistical software package (SPSS Inc, Chicago, IL, USA). The level of significance was set at $p < 0.05$ (2 tailed). Missing items were replaced using the expectation-maximization algorithm [37]. Concentrations of TNF-α, IL-6, and IL-33 were log transformed to approximate a normal distribution. Multivariate normality of the data distribution was tested using Mahalanobis distance with a level of significance of $p < 0.001$. To demonstrate patient characteristics, the sample was split into 2 groups with less (5–7 points) versus more intense pain (8–10 points). Pearson χ^2 and independent-sample *t* tests for categorical and continuous variables, respectively, were used to compare both groups on demographic and health characteristics. The Mann-Whitney *U* test was used for group comparisons on BMI, GRACE score, and peak troponin level, as these values were not normally distributed.

We used multivariate linear regression with forced entry of covariates to test for an independent contribution of pain levels to the concentrations of the assessed cytokines. Variables were added to the model in 5 blocks. In a first step, we entered the a priori defined control variables (age and gender). Depression and BMI were entered in a 2nd and the GRACE score in a 3rd step. In block 4, the ASDS sum score served as a psychometric control variable. Finally, pain was added to the model. For each cytokine, regression models were run separately. We did not adjust *p* values for multiple comparisons because of the prespecified direction of the association between pain and cytokine levels.

Linearity, homoscedasticity, and absence of multicollinearity were tested by scatter plot and curve estimation. Durbin Watson statistics assured exclusion of autocorrelation. Results are expressed as unstandardized *b* coefficients, standard errors of the mean, and changes in R^2 in each step with *p* values.

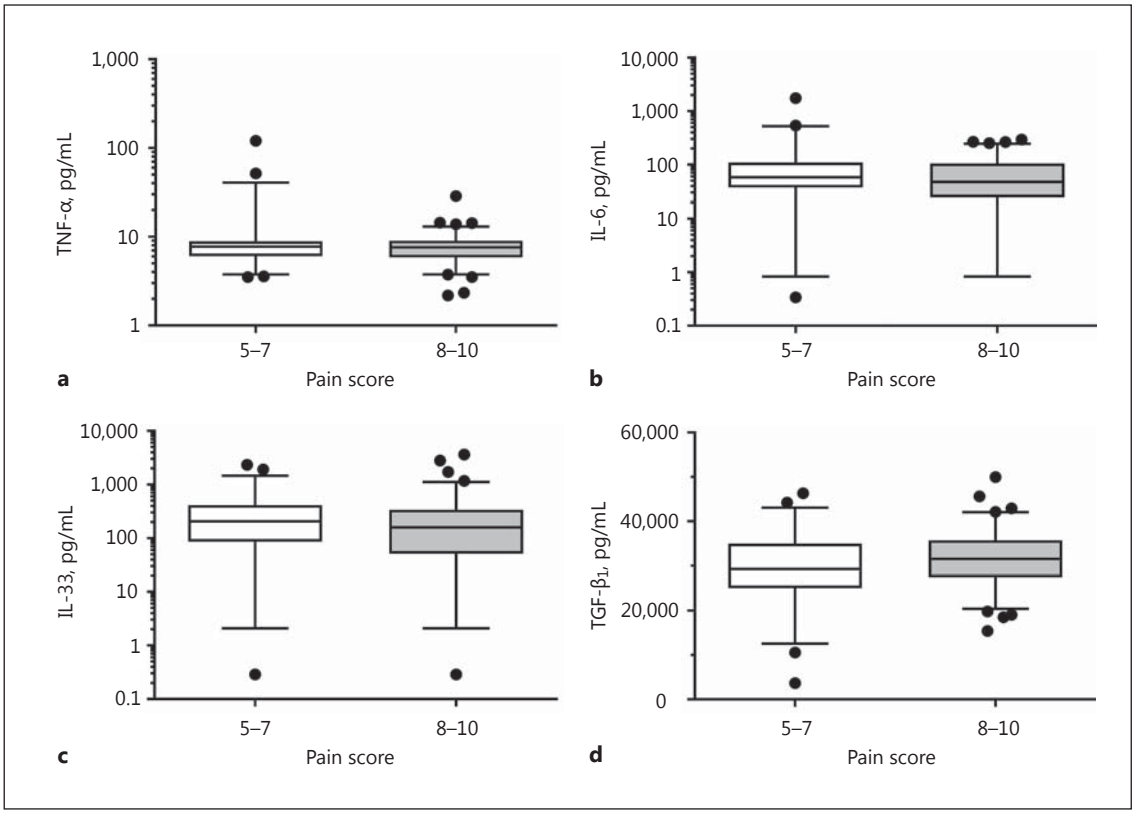

Fig. 1. Box plots of serum levels of cytokines TNF-α (**a**), IL-6 (**b**), IL-33 (**c**), and TGF-β_1 (**d**) grouped per less versus more intense pain (medians, interquartile ranges, whiskers at 5th and 95th percentiles).

Table 2. Cytokine assessments

Results	TNF-α	IL-6	IL-33	TGF-β
Quantifiable, *n*	140	132	119	140
Not quantifiable, *n*	0	7	19	0
Not detectable, *n*	0	1	2	0

Results

Patient Characteristics

Table 1 shows the patient characteristics of the total sample and both groups per pain level. The majority of patients were male. While few patients had had a previous MI, 1 out of 4 reported lifetime depression. The 2 groups did not differ significantly in age, gender distribution, and cardiac-related variables. Patients who experienced more pain were significantly more frequently living alone.

For illustrative purposes, cytokine values of both groups stratified according to the intensity of pain are shown in Figure 1. As shown in Table 2, most values were detectable.

Regression Analysis

Table 3 shows hierarchical regression models including the 4 cytokines as dependent variables.

TNF-α. Only lifetime depression was significantly and inversely associated with TNF-α concentration (p = 0.013). No significant association emerged for pain with TNF-α (p = 0.45).

IL-6. Higher BMI (p = 0.006) and a higher GRACE score (p = 0.003) were both associated with higher IL-6 concentrations. Pain was not associated with IL-6 (p = 0.23).

IL-33. Higher pain levels were significantly associated with lower IL-33 (p = 0.015). Pain explained an additional 4% of the variance in IL-33 concentration independently of all other covariates in the model. None of the other variables were significantly associated with IL-33.

Table 3. Regression analysis with TNF-α, IL-6, IL-33, and TGF-β_1 as outcome variables

	Step 1	Step 2	Step 3	Step 4	Step 5
TNF-α					
Model statistics (n = 140)					
ΔR^2	0.014	0.057	0.004	0.011	0.004
p value	0.384	0.040	0.061	0.059	0.080
Age	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Female gender	–0.01±0.05	0.03±0.05	0.03±0.05	0.03±0.05	0.04±0.05
Body mass index		0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Lifetime depression		*–0.11±0.04*	*–0.12±0.04*	*–0.11±0.04*	*–0.11±0.04*
GRACE score			0.00±0.00	0.00±0.00	0.00±0.00
ASDS sum score				–0.00±0.00	–0.00±0.00
Pain					–0.01±0.01
IL-6					
Model statistics (n = 140)					
ΔR^2	0.044	0.032	0.068	0.004	0.009
p value	0.044	0.029	0.001	0.001	0.002
Age	0.01±0.00	0.01±0.00	–0.00±0.01	–0.00±0.01	–0.00±0.01
Female gender	*–0.30±0.13*	*–0.30±0.13*	–0.23±0.13	–0.23±0.13	–0.21±0.13
Body mass index		0.02±0.01	*0.03±0.01*	*0.03±0.01*	*0.03±0.01*
Lifetime depression		0.11±0.11	0.08±0.11	0.07±0.11	0.08±0.11
GRACE score			*0.01±0.00*	*0.01±0.00*	*0.01±0.00*
ASDS sum score				0.00±0.01	0.00±0.01
Pain					–0.04±0.03
IL-33					
Model statistics (n = 140)					
ΔR^2	0.037	0.020	0.000	0.002	0.041
p value	0.075	0.092	0.158	0.225	0.047
Age	*–0.01±0.01*	*–0.01±0.01*	–0.01±0.01	–0.02±0.01	–0.02±0.01
Female gender	–0.04±0.19	–0.09±0.20	–0.10±0.20	–0.10±0.20	–0.05±0.20
Body mass index		–0.03±0.02	–0.03±0.02	–0.03±0.02	–0.02±0.02
Lifetime depression		0.06±0.17	0.06±0.17	0.08±0.17	0.10±0.17
GRACE score			0.00±0.00	0.00±0.00	0.00±0.00
ASDS sum score				–0.00±0.01	–0.01±0.01
Pain					*–0.11±0.04*
*TGF-β*1					
Model statistics (n = 140)					
ΔR^2	0.066	0.024	0.003	0.001	0.029
p value	0.010	0.012	0.021	0.038	0.014
Age	*–147.38±53.91*	*–127.59±54.58*	*–159.49±73.49*	*–163.26±74.67*	*–160.43±73.79*
Female gender	3,127.67±1,613.47	*3,377.93±1,659.54*	*3,560.01±1,686.564*	*3,550.28±1,692.54*	3,234.27±1,678.53
Body mass index		266.44±140.78	*289.01±145.33*	*290.79±145.92*	268.98±144.50
Lifetime depression		359.45±1408.18	300.43±1414.13	379.94±1440.99	179.08±1426.48
GRACE score			19.72±30.35	21.87±31.20	18.00±30.87
ASDS sum score				–18.78±59.38	–3.73±59.09
Pain					*770.91±369.95*

Data are shown as unstandardized b coefficients (means ± SEM). Results with $p < 0.05$ are in italics. ASDS, Acute Stress Disorder Scale; GRACE, Global Registry of Acute Coronary Events. Values <0.005 were approximated to 0.00.

TGF-β_1. Higher pain levels were associated with a higher TGF-β_1 concentration ($p = 0.031$), whereas older patients had lower TGF-β_1 ($p = 0.039$). Pain explained an additional 2.9% of the variance in TGF-β_1 concentration, independently of all other covariates in the model.

Discussion

The purpose of our study was to examine whether pain during AMI is related to inflammation, independent of demographic, medical, and psychometric factors. We found significant associations with levels of circulating anti-inflammatory cytokines but not with levels of proinflammatory cytokines.

More intense pain during MI was significantly associated with lower IL-33 levels. To the best of our knowledge, no study has previously examined circulating IL-33 during AMI and its relationship to pain or acute psychological distress. Since IL-33 was shown to have cardioprotective and anti-atherosclerotic properties in general [11], we interpret this relationship to reflect a path leading from more intense pain during AMI to poorer cardiac prognosis, although this assumption needs investigation in prospective studies. However, the potential consequences of lower circulating IL-33 levels during AMI are not unequivocal. While 2 studies found no prognostic significance of IL-33 [38, 39], 2 other studies in patients with STEMI reported increased mortality [28] and increased risk of recurrent MI [27] among those with high IL-33 levels. Further research is needed to evaluate the significance of decreased IL-33 in MI patients experiencing more pain.

We found a significant direct association between pain and the TGF-β_1 concentration. Only one study has previously examined TGF-β during AMI and its prognostic significance [40]. That study showed neither a difference in circulating TGF-β_1 concentrations between ACS patients and patients with stable coronary artery disease nor an association with recurrent MI and mortality. An increase in TGF-β_1 during AMI with greater pain intensity can therefore be assumed to have no negative effect on prognosis. TGF-β is known to be a significant mediator of nociception and to have protective effects against the development of chronic neuropathic pain [41]. The effect we found could therefore be part of a physiological counterregulation set off by acute pain.

We did not observe a significant association between pain and TNF-α during AMI. Since cardiac inflammation is also expected to produce TNF-α [8], a potential independent effect of pain or ASD on TNF-α levels might be superimposed by the acute phase response launched by myocardial damage.

We further found that neither pain nor ASD symptoms were significantly associated with IL-6 levels. A correlation, however, was observed for the GRACE score. This is in line with the previous literature showing that IL-6 is associated with increased morbidity and mortality after ACS [24–26]. We had hypothesized that pain or ASD would also be associated with IL-6, since it has previously been described as a predictor of posttraumatic stress disorder [42]. However, such a relationship may be too subtle compared to superimposed cardiac inflammation.

The characteristic course of the acute phase reaction during MI might be responsible for our nonsignificant results with regard to the proinflammatory cytokines. As mentioned above, cardiac inflammation during AMI can be divided in a first step, which is affected by proinflammatory cytokines and an inflammatory reaction to process and clear damaged tissue, and a second step, in which inflammation is suppressed by anti-inflammatory cytokines in order to initiate myofibroblast proliferation and scarring [7, 8]. It is possible that, due to the delay between onset of symptoms and blood sampling, we primarily examined the second phase. Therefore, in our samples, proinflammatory cytokines may already have been downregulated by anti-inflammatory mediators and thereby escaped detection in relation to pain intensity.

Cytokines also showed associations with other demographic and medical variables. IL-6 was directly associated with BMI. This has been found previously in, for instance, the CoLaus study [43]. TGF-β concentrations were lower in our younger study participants. Surprisingly, patients with lifetime depression had lower concentrations of TNF-α during AMI, although major depressive disorder has been associated with inflammation, including higher levels of TNF-α [44, 45].

Our data indicated that patients experiencing more pain were significantly more often living alone. Other demographic variables, i.e., age, gender, and BMI, were not associated with pain. Cardiac markers like peak troponin value, the number of coronary vessels affected, left ventricular ejection fraction, and the GRACE score did also not differ between both groups (high vs. low pain indications). Pain was therefore not primarily influenced by cardiac injury, an interpretation which is supported by previous data showing that chest pain considerably relates to psychological factors [46].

Our study has several limitations. We measured cytokine levels only once, which does not trace modeling of their trajectory during the acute phase of MI. Blood samples could be drawn within several days after MI onset, depending upon how quickly patients were admitted to the hospital and included in our study. Consequently, as cytokine concentrations change over time during AMI, our results were affected by the variability of the interval between onset of pain and blood sampling. Recall bias is possible, as, due to the study design, we assessed pain retrospectively and only approached patients who were hemodynamically stable, often after the acute coronary intervention. We included patients who experienced a significant amount of pain, which reduces the variability in pain scores and thus the chance of finding a significant association with cytokine levels, while also limiting generalizability of our results to patients with little or no pain. Due to the cross-sectional design of our study, we are unable to draw causal inferences. Cytokines have previously been discussed as transmitters of danger signals to the brain and thereby to induce sickness behavior [47, 48], and therefore an influence of cytokines on pain perception is also possible.

In summary, our study suggests that cytokines during AMI are not only reacting to myocardial ischemic tissue damage, they are also connected to the subjective experience of the situation reflected by pain intensity. We found an association between acute pain levels and IL-33 and TGF-β, 2 predominantly anti-inflammatory cytokines, in a cohort of patients with AMI. To the best of our knowledge, the currently available evidence does not allow a firm statement as to the clinical relevance in terms of increased morbidity and mortality of the observed relationships between pain and cytokine levels. However, as IL-33 has well-established atheroprotective functions and is beneficial for cardiac remodeling, its decrease in conjunction with pain might worsen the prognosis of patients with cardiac disease.

Disclosure Statement

The authors declare that there is no conflict of interest.

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